REMARKS

Status of the claims

Claims 1-190 were pending in the present application. By virtue of this response, claims 8-10, 12-23, 25-26, 29-32, 37-38, 41-45, 50, 61, 66, 71, 73, 80, 102-103, 110-114, 117-119, 121, 124-126, 131-134, 137-138, 141-145, 159, 164-165, 183-184, and 186-187 have been cancelled, claims 1-5, 7, 24, 27-28, 33, 35, 39, 49, 51-54, 57, 65, 67-70, 74, 76, 78, 84, 88-89, 98, 100, 105, 108, 115-116, 122-123, 127-128, 135, 139-140, 146, 149, 153, 160-163, 166, 182, and 189 have been amended and new claims 192-198 have been added. Accordingly, claims 1-7, 11, 24, 27-28, 33-36, 39-40, 46-49, 51-60, 62-65, 67-70, 72, 74-79, 81-101, 104-109, 115-116, 120, 122-123, 127-130, 135-136, 139-140, 146-158, 160-163, 166-182, 185, and 188-198 are currently under consideration.

The amendments to claims 1, 49, 65, and 108 are supported by the specification, for example, in paragraphs [0019], [0108], [0110]-[0012], [0135], and [0141]. The amendments to claims 84 and 149 are supported by the specification, for example, in paragraphs [0103] and [0105]. The amendments to claims 4 and 5 are supported by the specification, for example, in paragraph [0110]. The amendments to claims 7 and 24 are supported by the specification, for example, in paragraphs [0162]. The amendments to claims 35, 39, 57, 59, 76, 78, 100, 135, 139, and 162 are supported by the specification, for example, in paragraph [0145]. The amendment to claim 149 is supported by the specification, for example, in paragraph [0150]. New claims 191, 192, 195, and 196 are supported by the specification, for example, in paragraph [0144]. New claims 193, 194, 197, and 198 are supported by the specification, for example, in paragraph [0110]. Claims 2, 3, 27, 28, 33, 74, 88, 89, 98, 105, 107, 115-116, 127-128, 153, 160, 161, 162, 163, 182, and 189 have been amended to correct typographical and clerical errors. Claims 1, 51-54, 65, 67-70, 115-116 have been amended to change the term "hybrid" to "heteroduplex" for consistency with the language used in other claims in the claim set.

With respect to any claim amendments or cancellations, Applicants have not dedicated to the public or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to

pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Claim Rejections under 35 U.S.C. §103(a)

Claims 1-42, 46-60, 62-79, 81-103, 105-142, 146-165, 170-176, 177-182, 183, 184, 185, 186, and 188 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kurn, U.S. Patent No. 6,251,639 A1 ("Kurn"), in view of Lizardi, U.S. Patent No. 6,123,120 ("Lizardi"). Applicants respectfully traverse this rejection.

Neither Kurn nor Lizardi, nor the combination thereof, teaches all of the elements of the claimed invention, as required for a *prima facie* case of obviousness.

Independent claims 1, 49, 65, and 108 recite nucleic acid amplification methods that require the use of two different composite primers, a "first primer" and an "amplification primer." The first primer is a population of different composite primers each comprising an RNA portion and a 3' DNA portion, each having a 3' random sequence, and each having a sequence that is not hybridizable to the template polynucleotide under conditions in which the first primer hybridizes to the template polynucleotide. The first primer hybridizes to the template and is extended to produce a first primer extension product, and a second primer hybridizes to the first primer extension product to produce a second primer extension product, thereby generating a complex of first and second primer extension products with an RNA/DNA heteroduplex at one end. An agent that cleaves RNA from an RNA/DNA heteroduplex cleaves the RNA from the first primer in the complex of first and second primer extension products, producing a binding site for the amplification primer. The amplification primer, which comprises some of the sequence of the first primer, binds to complementary sequences on the second primer extension product, and amplification proceeds by a cyclic process of amplification primer binding, primer extension, and strand displacement.

Neither Kurn nor Lizardi teach or suggest an amplification method involving production of a complex of first and second primer extension products with an RNA/DNA heteroduplex at one

end that may be subsequently cleaved to enable binding of an amplification primer. Neither of these references teaches an amplification method in which two different types of composite primers are used, a population of different composite primers with random sequences for hybridization to the template and extension, and a second composite primer for amplification by extension and strand displacement, as claimed.

Kurn teaches use of a single composite primer having a sequence complementary to a polynucleotide target, and does not teach use of a population of primers with 3' random sequences as claimed. Kurn also does not teach production of a *second* primer extension product to form a complex of first and second primer extension products with an RNA/DNA heteroduplex at one end as claimed. Lizardi does not cure the defects of Kurn with respect to the presently claimed invention. Lizardi does not teach *any* composite primer, much less an amplification method that uses *two different* composite primers. Lizardi also does not teach a method in which a complex of first and second primer extension products is generated with an RNA/DNA heteroduplex at one end as the substrate for amplification. Thus, the combination of Kurn and Lizardi fails to teach all of the elements of independent claims 1, 49, 65, and 108, and by extension, claims dependent on these claims.

Independent claims 84 and 149 recite nucleic acid amplification methods that include the use of a single composite primer that hybridizes to a multiplicity of template polynucleotide sites and is also used as a primer for amplification. The same composite primer is used for both primer extension and amplification. The specification discloses parameters for composite primers that show partial sequence homology to a multiplicity of template polynucleotide sites, such as genomic DNA sequences. For example the NCBI Blast program can be searched for "short, nearly exact matches" as described in the specification (paragraph [0134]). An amplification method using a single composite primer that hybridizes to a multiplicity of polynucleotide sites is exemplified in Example 1.

Kurn does not teach an amplification method using a single composite primer that hybridizes to a multiplicity of template polynucleotide sites. Lizardi does not teach use of *any* composite primer. Lizardi teaches use of a "random *set* of primers" (see, *e.g.*, Abstract), *not* a

single primer that hybridizes to a multiplicity of template sites. Lizardi does not teach use of a single composite primer for both primer extension and amplification as claimed. In the presently claimed invention, a composite primer hybridizes to a multiplicity of template sites and is extended to form a substrate for amplification comprising an RNA/DNA heteroduplex. The RNA portion of the RNA/DNA heteroduplex, originally the RNA portion of the composite primer, is cleaved with an agent that that cleaves RNA from an RNA/DNA heteroduplex, creating a binding site for another molecule of the same composite primer, and composite primer hybridization, extension, and strand displacement are repeated from the same substrate to produce amplification products. Lizardi teaches a process of continuous random hybridization of a set of primers to the template and to primer extension products. Lizardi does not teach the production of a substrate for amplification that may be used repeatedly by the same primer for amplification as claimed. Thus, the combination of Kurn and Lizardi fails to teach all of the elements of independent claims 84 and 149, and by extension, claims dependent on these claims.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Claim 187 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kurn in view of Lizardi, in further view of Malek et al., U.S. Patent No. 5,712,127 ("Malek"). Claim 187 has been canceled herein, rendering this rejection moot.

Double Patenting

Claims 1 and 189 are rejected over Claims 9 and 266 of Kurn (U.S. Patent No. 6,946,251). Applicants would like to defer consideration of this issue until the Office indicates that the present claims are allowable.

Claims 1 and 189 are rejected over claims 1 and 77 of Kurn (U.S. Patent No. 6,692,918) or over claims 1 and 49 of Kurn (U.S. Patent No. 6,251,639), in view of Lizardi (U.S. Patent No.

6,124,120). Neither the cited claims of U.S. Patent No. 6,692,918 nor the cited claims of U.S. Patent No. 6,251,639 recite a first composite primer with random 3' sequences, production of a complex of first and second primer extension products with an RNA/DNA heteroduplex at one end as a substrate for amplification, or a composite amplification primer that is different from the first composite primer and hybridizes to the second primer extension product to effect amplification by primer extension and strand displacement, as recited in claim 1 of the present application, and by extension claim 189, which is dependent on claim 1. Lizardi also does not teach these claim elements, as discussed above. Thus, the claims of U.S. Patent No. 6,692,918, in combination with Lizardi, fail to render the presently claimed invention obvious.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the double patenting rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.492692001300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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